



Hamilton, A., Clissold, R. L., Inward, C., Caskey, F., & Ben-Shlomo, Y. (2017). Socio-demographic, psychologic health, and lifestyle outcomes in young adults on renal replacement therapy: systematic review. *Clinical Journal of the American Society of Nephrology*, 12(12), 1951-1961. <https://doi.org/10.2215/CJN.04760517>

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[10.2215/CJN.04760517](https://doi.org/10.2215/CJN.04760517)

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TITLE:

Socio-demographic, psychological health and lifestyle outcomes in young adults on renal replacement therapy: systematic review and meta-analyses

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INDEX WORDS:

Young adult, renal replacement therapy, kidney transplantation, dialysis, education, employment, relationships, mental health, quality of life, lifestyle, systematic review, meta-analysis

WORD COUNT

Abstract: 280

Main body: 3607

STRUCTURED ABSTRACT

Background and objectives: Young adults receiving renal replacement therapy (RRT) face additional challenges in life. The impact of established kidney failure on young adulthood is uncertain. We aimed to establish the psychosocial and lifestyle status of young adults receiving RRT.

Design, setting, participants, and measurements: Systematic review and meta-analysis of 16-30 year olds receiving RRT, compared with the general population. We selected randomized controlled trials, cohort or cross-sectional studies without language restriction and extracted proportions of socio-demographic and lifestyle outcomes; or validated psychological health tests producing quality of life, wellbeing and self-esteem scores. We undertook random-effects meta-analysis.

Results: 60 studies of 15575 participants. Studies were largely single center cross-sectional studies of those transplanted in childhood. Compared to healthy peers, young adults on RRT had lower quality of life, worse for dialysis patients (7 studies, standardized mean difference (SMD) -1.01, 95% confidence interval (CI) -1.32, -0.70) compared to transplant (9 studies, SMD -0.42, 95% CI -0.64, -0.20). They were more likely to be unemployed (7 studies, relative risk (RR) 1.89, 95% CI 1.47, 2.44) and to live in the family home (2 studies, RR 1.84, 95% CI 1.40, 2.43). They were less likely to be married or have a partner (4 studies, RR 0.71, 95% CI 0.53, 0.95). Higher education (3 studies, RR 1.05, 95% CI 0.73, 1.51), alcohol abstinence (3 studies, RR 1.96, 95% CI 0.84, 4.67) and smoking status (2 studies, RR 0.72, 95% CI 0.36, 1.44) did not differ. Results were limited by high heterogeneity and a small evidence base, biased towards surviving patients.

Conclusions: Established kidney failure is associated with lower quality of life in young people and limited employment, independence and relationships compared with healthy peers.

INTRODUCTION

Young adulthood is a distinct developmental period where physical growth stops yet high-level brain function continues to develop(1). Young adulthood features growing independence, decision-making, self-exploration and experimentation. Young adults receiving renal replacement therapy (RRT) in high-income countries are mostly transplanted (70% of United States 0-21 year olds(2) and 73% of United Kingdom 18-24 year olds(3)) and must learn to integrate responsibility for managing their condition into their changing lives.

There are little data regarding psychosocial outcomes for young adults, an area not captured by most disease registers. Whilst young adults are known to be high risk for graft failure(4, 5), the extent to which established kidney failure has affected their social status, mental health and lifestyle remains unclear. The literature to date focuses on single center cohorts of transplanted children followed to young adulthood, and the process of transition to adult services(6, 7). Those receiving dialysis, presenting directly to adult services and non-surviving patients are underrepresented.

We aimed to review the literature systematically to establish the socio-demographic, psychological health and lifestyle status of young adults receiving RRT. This information is important to determine whether patients lead comparable lives to their healthy peers. We hypothesized that young adults receiving RRT would be psychosocially disadvantaged compared to healthy peers.

MATERIALS AND METHODS

We conducted this systematic review in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria(8) rather than Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA), as it is more appropriate for observational studies. We did not use a review protocol.

Eligibility Criteria

We used the criteria defined in Table 1 to select studies from our systematic search. We included all studies reporting socio-demographic, psychological health and lifestyle outcomes for young adults (defined as aged between 16 and 30 years at the time of study) receiving long-term RRT. There is no consensual definition for young adulthood, and we chose a wide age-range to ensure we did not miss any important publications. We included all language types.

Search Strategy

Together with an Information Specialist, we devised a sensitive search strategy (supplementary material) which we applied to 9 databases (Medline, EMBASE, PsycINFO, Applied Social Sciences Index and Abstracts (ProQuest), CINAHL (EBSCO), Web of Science, Scopus, Open Grey, and Cochrane Library). We ran our first search in July 2015 and repeated the search in August 2016, for the latter limiting results to those from the last year only. We also screened references of key articles obtained in our search.

Where studies did not present appropriate data (e.g. subgroup data not presented, or study published in abstract form), we asked authors by email for the data if the study was carried out in the last five years; 2/5 study authors responded to these requests.

Study Selection, Data Collection, and Risk-of-Bias Appraisal

We imported all references into Endnote™ and then used this software to remove duplicate publications. AH screened the titles and abstracts of all citations to identify studies fulfilling the inclusion criteria. RC screened a random sample of 1000 titles and abstracts to ensure

consistency. Concordance was 99% and any disagreements were resolved by discussion. We used Google Translate™ to screen non-English abstracts and arranged formal translation of included non-English articles.

Where there were multiple versions of the same study, we selected the more comprehensive/substantive version (e.g. journal article over conference abstract, or journal articles arising from theses). We recorded study characteristics and used the Newcastle-Ottawa Scale (NOS) to assess the risk of bias for all studies(9). A high NOS score (range 0 - 9) indicates a lower risk of bias. AH assessed bias in all included studies. RC independently assessed bias in a random sample of six (10%) of the included studies to ensure a fair appraisal. Any disagreements were resolved by discussion.

Summary Measures and Synthesis of Results

We examined studies fulfilling the inclusion criteria and collated whether studies reported common outcome measures (regardless of scales used) before deciding on which outcome measures were amenable to meta-analysis. If a study presented multiple scales for a single outcome, we chose the most frequently used scale for analysis. We compared the data across studies and devised a data collection form to obtain consistently reported data. Study review and data extraction was performed by AH. RC independently extracted data from a random sample of six (10%) of the included studies to ensure consistency and accuracy. There was 100% concordance for data extraction.

Statistical Methods and Subgroup Analysis

For outcomes reported as proportions, we extracted these and calculated their 95% confidence intervals (CI) by assuming a binomial distribution using Wilson's method(10) as no study reported these. We then performed a meta-analysis of the outcome proportion using a random effects model (employing DerSimonian & Laird's method), as we presumed there

would be marked between-study heterogeneity given methodological differences. We visually examined effect estimates using forest plots and calculated heterogeneity statistics (I^2 and 95% CI using a non-central χ^2 based approach(11), τ^2). We did not stratify by modality at enrolment as most studies were long-term follow-ups of pediatric kidney transplant patients where current modality was not reported, or the outcome proportion by modality was not provided. However, most studies reporting quality of life scale scores did so by modality so one could compare sub-groups.

For studies with control data, papers reported a proportion/percentage outcome and sample size for the kidney sample and provided comparative control data mostly using census/routine survey data (no reported sample size in seven cases; number with outcome/total in three cases and the number with outcome/no total in one case). We converted outcome rates (95% CI) for the kidney sample as above. The statistics comparing the kidney sample to controls were limited; there was no comparison in six studies, the Chi-Square test in two studies, p-value only in two studies and a standardized incidence ratio and p-value in one study. Therefore where the reference sample size was unknown ($n=8$), we calculated the risk ratio (RR) (95% CI) by dividing study group risk by control group risk. This assumed no sampling variation for the larger reference population, as these are based on much larger samples and assume all the variability in the RR is determined by the sampling variability in the smaller clinical group. Our calculated RR matched the standardized incidence ratio where provided. Where the sample size was known ($n=3$), we accounted for reference population variability. We then inspected forest plots (log RR) and chose to undertake a random effects meta-analysis (as above) to derive the pooled RR (95% CI, I^2 statistic and 95% CI, τ^2).

Quality of life is often assessed using the SF-36 measure, which has four physical and four mental domains, or the EQ-5D, which weights five domains (anxiety, pain, mobility, usual activities, self-care) to produce a utility score with a maximum of 100. To summarize the

quality of life data to a single domain or utility score, we converted mean SF-36 domains to an overall utility score using a model (EQ1) developed by Ara and Brazier(12), regarded as the best approach in the absence of individual participant level data. This model was derived using ordinary least square regression models and weights each SF-36 domain to derive an EQ-5D utility score, as follows:

$$\begin{aligned} \text{EQ-5D utility score} = & 0.03256 + (0.0037 * \text{physical functioning}) + (0.0011 * \text{social function}) - \\ & (0.00024 * \text{role limitations due to physical problems}) + (0.00024 * \text{role limitations due to} \\ & \text{emotional problems}) + (0.00256 * \text{mental health}) - (0.00063 * \text{vitality}) + (0.00286 * \text{bodily pain}) \\ & + (0.00052 * \text{general health}) \end{aligned}$$

To derive the standard deviation (SD) for the utility score, we used the model-based approach developed by Wyld et al(13). This model derived a regression function using fractional polynomials of observed SDs against SDs from utility estimates in published studies, as follows:

$$\text{SD} = 0.368 - (0.82 * \text{utility score}^2) + (0.625 * \text{utility score}^3)$$

We confirmed the validity of this model by showing similar model-derived SDs and reported SDs in our extracted data. Because the utility score is numerical, we performed a random effects meta-analysis using Glass' method (which standardizes using the reference group SD) to pool standardized mean differences (SMD) using the mean scale score, SD and sample size for patient and control groups stratified by modality. We also used this approach for the non-SF-36 quality of life scales. We derived both the overall heterogeneity statistics (I^2 and 95% CI, τ^2) as well as assessing for subgroup (transplant versus dialysis) heterogeneity to test for an interaction. If studies did not report a normative comparator, we still included them in the meta-analysis if we were able to find appropriate country and age-specific control data (mean, SDs). We undertook several sensitivity analyses. We repeated the meta-analysis

excluding the studies with derived control data to see if this altered our results qualitatively. We also performed separate meta-analyses by modality. Stratifying by modality in some cases meant including two subgroups from the same study. This does not affect the point estimate as the data points were independent, but because the two subgroups come from the same study there is the potential for structural clustering, so that the standard errors for the pooled modality estimates may be underestimated. We investigated this by repeating the meta-analysis by modality but this time meta-analyzing the treatment-by-modality interaction in studies that reported data for both transplant and dialysis patients. We assessed for small study effects using funnel plots, comparing by modality and excluding studies that did not report normative comparators (to avoid artificially inflating the effect estimate sample size). To help the reader contextualize the SMD results, we used normative data from the 2012 Health Survey for England(14) and back-calculated the differences in the SMD for the kidney patients to an absolute EQ-5D utility using the reported SD.

For studies reporting other scale scores, we performed a random effects meta-analysis using the same methods as for the utility score analysis. We used Stata® 14 for our analyses.

RESULTS

Description of included studies

We included 60 studies in our quantitative review. We identified seven qualitative studies, which are not discussed further. Figure 1 demonstrates the results of our systematic searches, and table 2 details the characteristics of the included studies. Table 3 summarizes the study attributes, and highlights that most studies were small (median 42 participants, interquartile range (IQR) 25, 78), single center (75%), and cross-sectional (80%). Half the studies examined young people transplanted in childhood. Studies were mainly from high-income

countries (78%). Where reported, the recruitment, response rate and key variable completeness of the various study types was reasonably high. However, the response rate was not reported in two-thirds of surveys.

Risk of bias

The modified NOS scores are shown in Table 3. The risk of bias was higher in studies that did not report any normative comparator data. The overall scale median percentage score was 71% (IQR 50, 75). Since 80% of our identified publications were cross-sectional, they are subject to attrition bias, as patients who may have died over follow-up are by definition not included and hence the observed results may be biased towards better outcomes. Two-thirds of studies involved surveys and/or interviews, where engaged patients are more likely to take part (selection bias). In addition, given the subjective nature of many of the outcomes, there may be recall and interviewer bias. Two-thirds of studies involved transplant patients; half the studies only recruited participants on the basis that they were transplanted as children, so that young adults presenting later may be underrepresented. Most studies were European/North American, reflecting a geographical bias towards these healthcare systems. Three-quarters of studies involved convenience sampling from single centers; here, center performance and clinician motivation may also bias results.

Observed proportions

The pooled proportion estimates for socio-demographic, psychological health and lifestyle outcomes are shown in table 4. Socio-demographic outcomes were commonly reported. There was considerable heterogeneity which was unaffected by stratifying by modality at enrolment.

There were fewer studies examining psychological health, with depression or anxiety being most frequently reported, although there was marked heterogeneity. Most of the data were

pooled from three studies that studied transplant patients using the same questionnaire(15-17), and apart from depression/anxiety and body image, all the estimates were from studies examining transplant patients. The apparent disparity between suboptimal mental health and good satisfaction in other areas of life may be explained by the small number of studies, and patient modality.

In terms of lifestyle, there were again few studies and high heterogeneity for the proportions of those currently smoking, taking part in sports and abstaining from alcohol. Young adults appeared to live healthy lifestyles.

Outcomes relative to healthy controls

The pooled effect estimates of socio-demographic, psychological health and lifestyle outcomes compared to healthy controls are shown in table 5. Few studies presented normative comparison data and, when pooled, were very heterogeneous.

Young adults on RRT were more likely to be unemployed (8 studies, RR 1.89, 95% CI 1.47, 2.44) and to live in the family home (2 studies, RR 1.84, 95% CI 1.40, 2.43). They were less likely to be married/have a partner (4 studies, RR 0.71, 95% CI 0.53, 0.95). Higher education (3 studies, RR 1.05, 95% CI 0.73, 1.51), alcohol abstinence (3 studies, RR 1.96, 95% CI 0.84, 4.67) and smoking status (2 studies, RR 0.72, 95% CI 0.36, 1.44) did not differ.

Psychological health scales

Only 5/9 studies measuring quality of life in transplant patients reported normative comparison data, and similarly only 3/7 studies in dialysis patients (table 5). The study sample sizes were small, particularly for dialysis patients (median n=17). Heterogeneity was less when stratifying by modality but remained high. The SF-36 was the most frequently used scale (n=4). Seven studies reported relevant quality of life measures, which we could not include in the meta-analysis due to missing variability data (n=3) or control data (n=4).

Young adults on RRT had lower quality of life compared to their peers, which was worse for dialysis patients (7 studies, SMD -1.01, 95% CI -1.32, -0.70) compared to transplant (9 studies, SMD -0.42, 95% CI -0.64, -0.20) (figure 2). This equates to the following absolute differences in EQ-5D utilities: mean utility for 16-30 year olds (n=1333) from the Health Survey for England 2012 was 93 out of 100 (SD 14.7, 95% CI 92.2, 93.8)(14); the average adjusted score for transplant patients is 6.2 points lower at 86.8 (95% CI 83.6, 90.1) and 14.8 points lower at 78.2 (95% CI 73.6, 82.7) for dialysis patients. This modality effect was also seen when meta-analyzing the interaction terms (see table 5 footnote for data). We found no evidence for small study effects ($p=0.7$) but analysis lacked power as few studies were available for inclusion.

We found no differences in the Positive and Negative Affect Schedule (PANAS), and the Rosenberg Self-Image Scale and Self-Perception Profile for Adolescents though these were measured in few studies with small numbers of participants and subject to high heterogeneity. Five studies reported relevant self-concept, self-esteem or self-image scale measures, which we could not include in the meta-analysis due to missing information (n=2) or a lack of control data (n=3). Three studies reported coping via the use of different multi-domain scales and could not be combined in a meta-analysis.

DISCUSSION

Key findings

This systematic review establishes the negative social and psychological impacts (lower quality of life and limited employment, independence and relationships) of end-stage renal disease (ESRD) on young adults compared to healthy controls and highlights the limitations of existing research. We have found a marked drop in quality of life particularly for dialysis

patients compared to those transplanted. Young adults on RRT were also more likely to be unemployed despite a similar proportion having higher education as in the general population (based on only three studies). The effect estimates we present are likely to be biased towards better outcomes, as many studies examined transplant patients and may be subject to a healthy responder bias.

Comparison with existing studies

To our knowledge, this is the first quantitative systematic review of psychosocial and lifestyle outcomes for young adult RRT patients. We found a similar drop in quality of life for dialysis compared to transplant as a previous systematic review in an older adult population(13), however comparison is limited as we calculated a Z-score relative to the general population, whereas Wyld et al reported absolute utility scores.

Implications for research and clinical care

This meta-analysis has identified some areas of concern regarding the long-term socio-demographic and psychological outcomes for young adults with ESRD. However, one must be cautious in interpreting these results given the limitations highlighted below. These data, despite a small evidence base, suggests limited life chances and need further attention to establish how young adults receiving RRT function in society and potential barriers they may face to establishing successful employment, independent living and long-term relationships. It is possible that psychosocial outcomes may be more meaningful to patients than biochemical and intermediate outcomes often collected by registries. In the short term, we are undertaking a large-scale national multi-center study looking at a young adult population of all treatment modalities: the Surveying People Experiencing young Adult Kidney failure (SPEAK) study(18). The results may raise awareness in the clinical setting and shift the focus of outcomes onto those that matter most to patients, perhaps prompting disease registers to

collect patient-centered outcomes. Ideally, researchers should undertake a large, prospective cohort study collecting baseline data in childhood and with repeat outcome measure data that span the transition into adulthood as well as later life. Comparative longitudinal population data, using the same methods, should also be available to facilitate interpretation. Such a study would be costly, challenging and would take at least a decade to undertake but would provide a far more robust evidence base on the needs of this ESRD population.

Strengths and limitations

The strengths of this review are the wide search criteria to ensure all relevant studies were included, the inclusion of grey literature and non-English articles, and repeating the systematic search to capture new studies. Furthermore, we have gone to great lengths not to lose valuable data by contacting authors for other data, converting different outcomes to a common metric and searching appropriate comparative data to provide additional measures of outcome differences.

There are also limitations to be consider. Firstly, the evidence base was small. Secondly, in some cases we had to assume no sampling variation in reference populations of unreported size. This results in artificially small CIs around the difference. Nonetheless, in all cases where this assumption was made, the normative data was based on census data or regional/national statistics, so this is a minor issue. Thirdly, pooled proportions come from different studies and therefore may not always be directly comparable due to reporting differences. Fourthly, we combined mean domain scores into a single EQ-5D utility score for the SF-36 quality of life studies. Although we used established methods for this conversion and calculating the score variability, these were validated in other datasets; however, where data were available the predicted values appeared consistent with the observed. Fifthly, many studies did not report sub-groups data, such as gender and modality (except for quality of

life), so we could not examine these variables for heterogeneity. Given the paucity of studies, we did not feel that exploration of between-study variability using meta-regression would have been helpful; in addition, we were reassured that subgroups were statistically (but not structurally) independent when including subgroups as individual studies in meta-analysis. Finally, as there were almost 20,000 abstracts to screen, we only checked a random sample of 1000 abstracts (5%) for inclusion and six studies (10%) for independent data extraction though concordance rates were high in both cases.

Quantitative assessment of bias

The nature of the studies in this area was such that we could only quantitate bias by modifying the NOS. For studies without comparator data, this lessened the scope of the bias assessment and the risk of bias was higher. However overall study quality appeared reasonable. In addition to the NOS, we summarized the study attributes in table 3 and described the potential bias that these attributes suggest.

Justification of exclusion

We excluded studies where outcomes were reported by caregiver/family/health or educational professionals to focus on the patient experience, particularly from a psychological perspective. Other reasons that studies were excluded are included in figure 1 - largely due to the reported average age of participants being outside the specified range.

Assessment of quality of included studies

The Oxford Centre for Evidence-based Medicine(19) grades evidence from level 1a (e.g. homogenous systematic review) to 5 (e.g. expert opinion without critical appraisal), and grades recommendations based on such evidence from level A (consistent level 1 studies) to D (inconsistent/inconclusive or level 5 evidence). According to this framework, overall the studies in this review are from level of evidence 2b to 4 and grade of recommendation B/C.

In general, studies were descriptive, cross-sectional and single center with small numbers of participants. There were no prospective studies though three studies were retrospective cohort studies. Whilst a third of studies presented normative data, these almost all used data collected for other purposes.

Generalization of the conclusions

Our review included young adults requiring RRT, and studies appropriately focused on transplant patients as they represent much of this age group in high-income countries where the studies were mostly undertaken. Therefore, the effect estimates we have presented are generalizable to transplant patients in high-income countries, but apart from quality of life may not be generalizable to young adults receiving dialysis. The small number of studies and high heterogeneity of findings must also be stressed, as well as the inability to explore demographic effects.

In summary, young adults receiving RRT have lower quality of life and limited employment, independence and relationships compared to healthy controls. This review highlights the limitations of existing research and clarifies the key patient-reported outcomes to focus on in the future.

ACKNOWLEDGEMENTS

We would like to thank Penny Whiting for help in planning this review. We thank Dee Knipe, Mairead Murphy and Penny Whiting for their help with creating and managing a database for references. We gratefully acknowledge Catherine Borwick, specialist librarian, for assistance with the search strategy. We sincerely thank the inter-library loan service at the University of Bristol and study authors for providing full-text articles. We are indebted to Heide Busse for German translation, Steve Clissold and Keisuke Suzuki for help with Japanese translation, José López-López for Spanish translation and Marta Tazewell for Polish translation. We also thank Professor Julian Higgins for advice on statistical aspects.

Support: AH is funded on a Tony Wing clinical studentship from the British Kidney Patient Association and Kidney Research UK. Funders had no role in study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Contributions: research idea and study design: all; data acquisition: AH & RC; data analysis/interpretation: all; statistical analysis: AH, YBS; supervision or mentorship: YBS, FC, CI. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. AH takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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TABLES

Table 1. Systematic search criteria

	Inclusion criteria	Exclusion criteria
Population	Young adults aged between 16 and 30 years at the time of study	Average age of study participants <16 or >30 years, incalculable or not reported
Exposure	End stage renal disease requiring transplantation, hemodialysis or peritoneal dialysis	Chronic kidney disease not requiring renal replacement therapy; acute kidney injury
Outcome	Socio-demographic (e.g. education, employment, income, living situation, relationships) Psychological health (e.g. quality of life, wellbeing, depression, anxiety) Lifestyle (e.g. alcohol, tobacco, illicit drug use, participation in sport, antisocial behavior)	
Study types	Randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, ecological studies, qualitative studies	Outcomes not self-reported, e.g. study of caregiver or clinician
Publication types	Abstract and full text articles, theses, book chapters Any language Any year	Editorials, reviews, case reports

Table 2. Characteristics of studies included in quantitative synthesis, by year

First author	Year	Country	Article type	Purpose	Number of participants	Average age at enrolment (years±SD)	Modality at enrolment	Average age at RRT start (years±SD)	Design ^a	Sampling method	Recruitment/response rate/key variable completeness	Funding	Control data source
Cross sectional studies with control data													
Ehrich (20)	1992	Europe	Journal article	Survey to establish schooling, employment and social status in young adult RRT patients	617	21-35	RRT	not reported	Descriptive	Registry (international)	617/864 surviving and not lost to follow-up (survey)	Grants (government, national societies and industry)	Age matched general population in France, Germany, UK, Italy and Spain, n not reported
Prather (21)	1992	USA	Thesis	Investigate whether medication adherence is related to psychosocial and family factors	41	16±2	Transplant	4±2 years post-transplant	Descriptive	Convenience, single center	not reported	Not reported	Age and sex matched US high school students, n not reported
Ayonayon (22)	1997	USA	Thesis	Examine personal and family coping style, self-image, and general life adjustment in those transplanted in childhood	45	30	Transplant	11	Descriptive	Convenience, single center	46/108 (survey)	Research grant	Age matched US census data, n not reported
Querfeld (23)	1997	Germany	Journal article	Long-term observation of pediatric RRT recipients	30	25±4	RRT	(duration 13 years)	Descriptive	Convenience, single center	30/33 surviving and not lost to follow-up (interview)	Not reported	Age matched German regional statistics, n not reported
Offner (24)	1999	Germany	Journal article	Long-term observation of pediatric kidney transplant recipients	124	25	Transplant	12±3	Descriptive	Convenience, single center	120/120 surviving and not lost to follow-up	Not reported	Age matched German regional statistics (25-35 years), n not reported
Wingen (25)	1999	Germany	Journal article	Long-term follow-up of pediatric kidney transplant patients	117	22	Transplant	12±3	Descriptive	Convenience, single center	123/123 surviving and not lost to follow-up	Not reported	Age matched German general population, n not reported
Olausson (26)	2001	Sweden	Journal article	Long-term follow-up of pediatric kidney transplant patients	28	23	Transplant	12	Descriptive	Convenience, single center	28/32 (interview)	Research grant and charity grant	Young adults with ulcerative colitis, n=33
Rosenkranz (27)	2005	Germany	Journal article	Assess vocational rehabilitation and quality of life in adult patients with early onset of ESRD	39	26±6	RRT	not reported	Descriptive	Convenience, single center	39/192 (participated in survey/eligible)	Not reported	Age matched German regional statistics, n not reported
de Castro (28)	2007	Spain	Journal article	To examine psychological adaptation in young adults transplanted in childhood	13	19	Transplant	not reported	Descriptive	Convenience, three centers	not reported	Not reported	Other solid organ transplants, n=11
Kärrfelt (29)	2008	Sweden	Journal article	To describe long-term psychosocial outcome after kidney transplantation during childhood	42	25	Transplant	not reported	Descriptive	Convenience, single center	42/68 (interview)	Not reported	Age matched Statistics Sweden data, n not reported
Aasebo (30)	2009	Norway	Journal article	Describe the life situation and lifestyle and quality of life of young adult kidney transplant recipients	131	29±4	Transplant	24	Descriptive	Registry (national)	131/280 (survey)	Not reported	Age matched regional Norwegian health survey data, n=2360
Riaño-Galán (31)	2009	Spain	Journal article	Investigate health-related quality of life in a group of children and adolescents with ESRD	81	16±3	RRT	10±4	Descriptive	Multicenter; 5/10 pediatric nephrology centers	81/82 (survey)	Research grant	Age matched Spanish schoolchildren, n=901
Rafie (32)	2011	USA	Thesis	To identify psychosocial issues	46	24±4	Transplant	19±5 (age at transplant)	Descriptive	National recruitment via internet	not reported	Not reported	Healthy high school children, n=458; chronically ill study participants, n=2987
Rocha (33)	2011	Portugal	Journal article	Assess the socio-demographic situation of adult-aged kidney-transplanted children	91	26±5	Transplant	13±2 (age at transplant)	Descriptive	Convenience, single center	91/91 surviving and not lost to follow-up	Not reported	Age matched Portuguese census data, n not reported
Ritchie (34)	2012	Australia	Journal article	Description of demographic characteristics of a cohort of young adults on RRT	495	22	RRT	16	Analytic, observational	Registry (national)	489/495 on remoteness variable	Not reported	Australian official statistics, n not reported
Mekahli (35)	2014	UK	Journal article	To assess the long-term quality of life of young adults treated with dialysis or transplantation since childhood	41	19±2	RRT	4	Descriptive	Convenience, single center	41/41 surviving and not lost to follow-up	Not reported	Age matched UK health survey data and official statistics (16–24 years), n not reported
Mellerio (36)	2014	France	Journal article	Assess the socio-professional situation of adult-aged kidney-transplanted children	374	27	Transplant	not reported	Descriptive	Registry (national)	374/624 (survey)	Industry grant	Age and sex matched French national statistics, n not reported
Cohort studies with control data													
Reynolds (37)	1993	UK	Journal article	Assess social adjustment in survivors of a pediatric RRT program	45	24±3	RRT	14	Analytic, observational	Convenience, single center	45/50 (interview)	Not reported	Age and sex matched UK control group, n=48
Morton (38)	1994	UK	Journal article	Assess lifetime psychiatric adjustment in survivors of a pediatric RRT program	45	24±3	RRT	14	Analytic, observational	Convenience, single center	45/50 (interview)	Not reported	Age and sex matched UK control group, n=48
Groothoff (39)	2003	The Netherlands	Journal article	To determine quality of life in young adults with ESRD since childhood	135	29	RRT	10	Analytic, observational	Registry (national)	135/187 (survey)	Funded by the Dutch Kidney Foundation	Age matched healthy Dutch control group (18–44 years), n=551
Longitudinal studies with control data													
Haavisto (40)	2011	Finland	Journal article	Long-term follow-up of pediatric kidney transplant patients	21	21	Transplant	2 years (age at transplant)	Observational	Convenience, single center	21/30 (interview)	Research grant	Age matched Finnish health survey, n=427
Studies without control data													
Fine (41)	1978	USA	Journal article	Long-term follow-up of pediatric kidney transplant patients	69	not reported	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	54/54 surviving and not lost to follow-up	Not reported	
Poznanski (42)	1978	USA	Journal article	Long-term follow-up of pediatric kidney transplant patients	18	16	Transplant	12	Descriptive, cross sectional	Convenience, single center	not reported	Not reported	
Velasco de Parra (43)	1980	Mexico	Journal article	Evaluate social and psychological status in childhood RRT patients	8	20	Transplant	8	Descriptive, cross sectional	Convenience, single center	15/15 surviving and not lost to follow-up	Not reported	
Simmons (44)	1987	USA	Book chapter	Long-term follow-up of pediatric kidney transplant patients	33	19-24	Transplant	Childhood	Observational, longitudinal	Convenience, single center	100/100 surviving and not lost to follow-up	Not reported	
Lee (45)	1989	USA	Journal article	Long-term follow-up of pediatric kidney transplant patients	30	(10 year follow-up)	Transplant	5-18 (age at transplant)	Descriptive, cross sectional	Convenience, single center	30/30 surviving and not lost to follow-up	Not reported	
Sato (46)	1990	Japan	Journal article	Long-term follow-up of pediatric kidney transplant patients	32	20	RRT	11 (age at transplant)	Observational, longitudinal	Convenience, single center	unknown	Not reported	
Morel (15)	1991	USA	Journal article	Long-term follow-up of pediatric kidney transplant patients	57	26±5	Transplant	10±5	Descriptive, cross sectional	Convenience, single center	57/57 surviving and not lost to follow-up	Research grant	
Roscoe (47)	1991	Canada	Journal article	Medical and social outcomes in adolescents with ESRD	90	22	RRT	14	Descriptive, cross sectional	Convenience, single center	90/96 (info available for 90 survivors)	Not reported	
Bochenska (48)	1992	Poland	Journal article	Assess emotional status in young adults on HD	5	18	HD	(duration 1 year)	Observational, longitudinal	Convenience, single center	not reported	Not reported	
Gämperli (49)	1996	Germany	Journal article	Long-term observation of pediatric kidney transplant recipients	37	28	Transplant	12	Observational, longitudinal	Convenience, single center	37/37 surviving and not lost to follow-up	Not reported	

Park (50)	1996	South Korea	Journal article	Long-term follow-up of pediatric kidney transplant patients	20	18 (approx.)	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	20/27 (interview)	Not reported
Krmar (16)	1997	Argentina	Journal article	Assess long-term rehabilitation and quality of life after kidney transplantation	17	23 (approx.)	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	17/18 (survey)	Not reported
Haberal (51)	2000	Turkey	Journal article	Long-term follow-up of pediatric kidney transplant patients	12	(5 year follow-up)	Transplant	14±2 (age at transplant)	Descriptive, cross sectional	Convenience, single center	27/40 surviving and not lost to follow-up	Not reported
Fernandez de Preliasco (52)	2002	Argentina	Journal article	Analysis of associations with compliance	74	16±1	Transplant	4±2 years post-transplant	Descriptive, cross sectional	Convenience, single center	74/74 surviving and not lost to follow-up	Not reported
Kobayashi (53)	2003	Japan	Journal article	Assess quality of life in pediatric RRT patients	156	19	RRT	13	Descriptive, cross sectional	Registry (national)	unknown	Research grant
Penkower (54)	2003	USA	Journal article	Describe the prevalence of psychological distress in adolescent transplant patients	22	16±1	Transplant	not reported	Observational, longitudinal	Convenience, single center	22/24 (interview)	Research grant
Cetingok (55)	2004	USA	Journal article	Assess quality of life by age group in kidney transplant patients	51	18-29	Transplant	not reported	Observational, longitudinal	Convenience, single center	not reported	Research grant
Feinstein (56)	2005	Israel	Journal article	To evaluate factors influencing adherence in kidney transplant recipients	79	(median 4 year follow-up)	Transplant	11 (age at transplant)	Descriptive, cross sectional	Convenience, single center	not reported	Not reported
Wu (57)	2007	China	Journal article	Long-term observation of pediatric kidney transplant recipients	20	24±5	Transplant	14±1 (age at transplant)	Descriptive, cross sectional	Convenience, single center	20/20 surviving and not lost to follow-up	Research grant
Ferraresso (58)	2008	Italy	Journal article	Long-term observation of pediatric kidney transplant recipients	36	26±6	Transplant	12±5 (mean age at first transplant)	Observational, longitudinal	Convenience, single center	35/35 surviving and not lost to follow-up	Research grant
Tielen (59)	2008	The Netherlands	Journal article	Identify health attitudes in young adult kidney transplant patients	26	22.5	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	26/44 without intellectual disability	Not reported
El-Husseini (17)	2010	Egypt	Journal article	To evaluate the effects of gender on health-related quality of life and health status in pediatric kidney transplants	77	19±3	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	77/77 surviving and not lost to follow-up	Not reported
Schiavelli (60)	2010	Argentina	Journal article	Explore satisfaction with transition	20	27	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	20/20 surviving and not lost to follow-up	Not reported
Feinstein (61)	2011	Israel	Conference abstract	Service evaluation of continuing pediatric nephrology follow-up for young adults transplanted in childhood	64	23±5	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	not reported	Not reported
Tay (62)	2011	Singapore	Journal article	Compare health-related quality of life in pediatric RRT patients	29	17±2	RRT	not reported	Descriptive, cross sectional	Convenience, single center	29/31 (survey)	Not reported
Haddiya (63)	2012	Morocco	Journal article	Report experience of PD in young patients aged under 20 years	8	16±2	PD	not reported	Descriptive, cross sectional	Convenience, single center	8/8 surviving and not lost to follow-up	Not reported
Tozzi (64)	2012	Italy	Journal article	Assess quality of life in young adults with a transplant and childhood ESRD	66	23	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	66/86 (interview)	Not reported
Sattoe (65)	2013	The Netherlands	Journal article	Effects of a peer support program on young adults with ESRD	24	20±3	RRT	not reported	Analytic, observational, cross sectional	Convenience (camp for young people with ESRD)	24/52 (survey)	Funded by the Dutch Kidney Foundation
Tong (66)	2013	Australia	Journal article	To elicit quality of life in adolescents and young adults with chronic kidney disease	14	17	RRT	not reported	Descriptive, cross sectional	Multicenter; 5 pediatric nephrology centers and 1 adult center	27/30 (interview)	Research grant
Gralla (67)	2014	UK and USA	Conference abstract	Assess education and career achievements in young adults with ESRD	31	25	Transplant	22	Descriptive, cross sectional	Not reported	not reported	Not reported
Johns (68)	2014	USA	Journal article	To examine socio-economic and racial differences in mortality in young adults receiving dialysis	11027	25±3	Dialysis	not reported	Analytic, observational, cross sectional	Registry (national)	10986/11027	Research grant
Lewis (69)	2014	UK	Journal article	Cross sectional survey of young adult RRT patients	296	25	RRT	17	Descriptive, cross sectional	Multicenter; 12 adult and 2 pediatric kidney units	296/931 (survey)	Not reported
Murray (70)	2014	UK	Journal article	Assess education and career achievements in young adults with ESRD	55	23	RRT	not reported	Descriptive, cross sectional	Convenience, single center	64/112 (survey)	Charity grant
Connelly (71)	2015	USA	Journal article	Assess non-adherence in a cohort of pediatric kidney transplant patients	175	23±6	Transplant	12±5	Observational, longitudinal	Convenience, single center	175/175 not lost to follow-up	Not reported
Gralla (72)	2015	UK and USA	Conference abstract	Compare ESRD impact on education and employment between UK and USA	54	25	Transplant	23	Descriptive, cross sectional	Convenience, dual center	not reported	Database supported by research grant
Lewis (73)	2015	UK	Journal article	Explore effect of RRT on education and employment transitions in young adults	35	20-30	RRT	under 19	Descriptive, cross sectional	Multicenter - 14 hospitals	35/931 (interview)	None
Massey (74)	2015	The Netherlands	Journal article	To investigate factors related to well-being and adherence amongst young adult kidney transplant recipients	62	25±2	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	62/84 (interview)	None
Patel (75)	2015	Belarus	Conference abstract	Compare ESRD impact on education and employment between UK and Belarus	20	23	Transplant	not reported	Descriptive, cross sectional	Convenience, single center	not reported	Not reported
Rus (76)	2015	Slovenia	Conference abstract	Long-term follow-up of pediatric kidney transplant patients	25	not reported	Transplant	16 years (age at transplant)	Descriptive, cross sectional	Convenience, single center	25/25 (interview)	Not reported

SD – standard deviation; RRT - renal replacement therapy; USA - United States of America; UK - United Kingdom; ESRD - end stage renal disease; HD - hemodialysis; PD - peritoneal dialysis

^aAccording to The Centre for Evidence Based Medicine, University of Oxford, UK(77)

Table 3. Summary features of studies included in quantitative synthesis

Study attributes	n	%	Study attributes (continued)	Summary statistic
Geography			Median (IQR) Newcastle Ottawa Quality Assessment Scale score^a	
Europe	30	50	Studies with control data (maximum score 7 points, n=21)	5 (5, 5)
North America	13	22	Studies without control data (maximum score 4 points, n=39)	2 (2, 3)
Asia	7	12	All studies with score as percentage	71% (50, 75)
South America	4	7	Year	
Australasia	2	3	Range	1978 to 2015
International (UK and USA)	2	3	Mean±SD	2004±10
Africa	2	3	Median (IQR)	2007 (1997, 2012)
Publication type			Number of participants	
Journal article	51	85	Range	5 to 11027
Conference abstract	5	8	Mean±SD	260±1418
Thesis	3	5	Median (IQR)	42 (25, 78)
Book chapter	1	2	Recruitment/response rate or key variable completeness (%)	
Study design			Recruitment for long-term observation studies (n=19)	
Cross sectional	48	80	Not reported/unknown	2
Cohort study or clinical cohort	12	20	Median (IQR)	100 (100, 100)
Study sampling method			Recruitment for interview studies (n=14)	
Convenience, single center	45	75	Not reported/unknown	3
Registry	7	12	Median (IQR)	82 (70, 90)
Multicenter	6	10	Response rate for survey studies (n=12)	
National recruitment via internet	1	2	Not reported/unknown	8
Not reported	1	2	Median (IQR)	59 (44, 83)
Study subject original modality			Key variable completeness for registry studies (n=2)	
Transplant	39	65	Not reported/unknown	0
RRT	18	30	Median (IQR)	99 (99, 100)
HD	1	2		
Dialysis	1	2		
PD	1	2		
Control data	21	35		

RRT – renal replacement therapy; HD – hemodialysis; PD – peritoneal dialysis; SD – standard deviation; IQR – interquartile range

Not all percentages add up to 100 due to rounding.

^aWe used this tool to assess bias in all study types, and modified it by omitting points where not applicable. For all studies, we omitted points for ‘Demonstration that outcome of interest was not present at start of study’ and ‘Was follow-up long enough for outcomes to occur’. For uncontrolled studies, we also omitted points for ‘Selection of the non-exposed cohort’ and ‘Comparability’. We compared total scores by study type and compared all studies using percentage scores

Table 4. Pooled proportion estimates and confidence intervals from weighted meta-analysis of observational studies, by study numbers and size, with heterogeneity statistics

Outcome	n	Number of studies	Proportion (95% CI)	I ² , % (95% CI)*	τ ²	Studies
Education and employment						
Working	2281	35	0.47 (0.40, 0.53)	90 (87, 92)	0.03	(15-17, 20, 22-27, 29, 32, 33, 35-37, 41, 42, 45, 46, 48-51, 57, 60, 61, 63, 64, 67, 70, 72, 73, 75, 76)
Unemployed	1705	29	0.19 (0.16, 0.22)	66 (46, 76)	0.005	(15-17, 22-26, 29, 30, 32, 33, 35-37, 41, 42, 44-49, 51, 61, 67, 70, 73, 75)
Studying	1471	26	0.29 (0.23, 0.36)	91 (89, 93)	0.03	(15, 17, 22-26, 29, 32, 33, 35-37, 41, 42, 46, 48, 50, 51, 61, 63, 64, 67, 70, 73, 75)
Higher education	1815	21	0.26 (0.18, 0.34)	95 (93, 96)	0.03	(15-17, 20, 22, 23, 26, 29, 30, 32, 33, 36, 40, 41, 49, 51, 54, 55, 67, 70, 76)
Have a disability or registered disabled	1252	13	0.15 (0.09, 0.20)	87 (79, 91)	0.008	(23, 24, 26, 29, 33, 35-37, 44, 49, 69, 70, 72)
Basic/manual job	366	5	0.44 (0.28, 0.59)	88 (72, 93)	0.03	(23, 24, 33, 36, 37)
Relationships and living arrangements						
Married/with partner	1811	26	0.25 (0.19, 0.31)	90 (87, 92)	0.02	(15-17, 20, 22, 23, 25, 26, 29, 30, 33, 35, 37, 41, 42, 45, 49-51, 55, 57, 58, 61, 64, 74, 76)
Live in family home	2357	24	0.56 (0.48, 0.64)	94 (93, 95)	0.04	(15-17, 20, 22-27, 29, 33, 35-37, 47, 49, 51, 59, 64, 67, 69, 73, 74)
Lives in urban area	11724	4	0.67 (0.48, 0.87)	99 (99, 99)	0.04	(34, 52, 68, 71)
Psychological health						
Depression/anxiety	449	13	0.30 (0.20, 0.40)	88 (82, 92)	0.03	(15, 17, 29, 32, 38, 42-45, 48, 54, 56, 67)
Self-rated health excellent or good	243	6	0.85 (0.76, 0.93)	74 (16, 87)	0.008	(15-17, 29, 45, 50)
Dissatisfied with body image	314	5	0.30 (0.16, 0.44)	88 (71, 93)	0.02	(15, 27, 29, 30, 37)
Satisfied with life	151	3	0.88 (0.83, 0.93)	0 (0, 73)	<0.001	(15-17)
Normal health, no complaints	151	3	0.55 (0.42, 0.68)	59 (0, 86)	0.007	(15-17)
Satisfied with personal relationships	151	3	0.76 (0.56, 0.96)	89 (61, 95)	0.03	(15-17)
Health never/seldom affects social life	151	3	0.72 (0.53, 0.92)	86 (38, 94)	0.02	(15-17)
Family support						
Satisfied with family support	300	6	0.79 (0.69, 0.89)	81 (53, 90)	0.01	(15-17, 52, 56, 67)
Disease never/seldom affects family life	151	3	0.80 (0.51, 1.08)	96 (93, 98)	0.06	(15-17)
Sexual function						
Satisfied with sex life	178	4	0.53 (0.30, 0.77)	92 (82, 95)	0.05	(15-17, 29)
Health no obstacle to sex life	120	2	0.46 (0.37, 0.54)	0	<0.001	(15, 17)
Lifestyle						
Current smoker	11580	4	0.17 (0.07, 0.28)	96 (93, 97)	0.01	(30, 36, 64, 68)
Participate in sports	274	4	0.46 (0.26, 0.67)	92 (82, 95)	0.04	(17, 30, 35, 76)
Sees friends or relatives at least weekly	176	4	0.84 (0.78, 0.91)	27 (0, 76)	0.001	(15-17, 76)
Abstains from alcohol	536	3	0.30 (0.03, 0.57)	98 (97, 99)	0.05	(30, 36, 38)
Has a driving license	501	3	0.65 (0.61, 0.69)	0 (0, 73)	<0.001	(25, 36, 64)
Attends social events at least weekly	134	2	0.56 (0.43, 0.70)	64	0.006	(15, 17)

CI – confidence interval

*CI for I² incalculable with one degree of freedom.

Table 5. Pooled relative risk and standardized mean difference estimates and confidence intervals from weighted meta-analysis relative to healthy controls, by study numbers and size, with heterogeneity statistics

Outcome	n	Number of studies	Effect estimate (95% CI)	I ² , % (95% CI)*	τ ²	Studies
Socio-demographic			<u>Risk Ratio</u>			
Unemployed	733	8	1.89 (1.47, 2.44)	49 (0, 76)	0.06	(20, 23, 24, 27, 29, 33, 35-37)
Married/with partner	594	4	0.71 (0.53, 0.95)	81 (21, 91)	0.06	(20, 22, 30, 36, 37)
Higher education	395	3	1.05 (0.73, 1.51)	81 (26, 91)	0.1	(22, 29, 36)
Live in family home	418	2	1.84 (1.40, 2.43)	40	0.02	(36, 37)
Lifestyle						
Alcohol abstainer	536	3	1.96 (0.84, 4.67)	90 (67, 95)	0.5	(30, 36, 38)
Current smoker	487	2	0.72 (0.36, 1.44)	94	0.2	(30, 36)
Psychological health			<u>SMD</u>			
Quality of life ^a	678	10	-0.65 (-0.88, -0.43)	83 (74, 88)	0.2	(30, 31, 35, 39, 40, 53, 62, 65, 66, 72); control data from (78-81)
Transplant ^{b, c}	517	9	-0.42 (-0.64, -0.20)	77 (54, 86)	0.09	(30, 31, 35, 39, 40, 53, 62, 65, 72); control data from (78, 79, 81)
Dialysis ^c	161	7	-1.01 (-1.32, -0.70)	62 (0, 81)	0.1	(31, 35, 39, 53, 62, 65, 66); control data from (79-81)
Positive affect ^d	121	3	0.40 (-0.12, 0.91)	84 (15, 93)	0.2	(28, 32, 74)
Negative affect ^d	121	3	0.18 (-0.26, 0.61)	79 (12, 90)	0.2	(28, 32, 74)
Self-perception/self-image ^e	86	2	-0.31 (-1.08, 0.47)	84	0.3	(21, 38)

SMD - standardized mean difference; CI - confidence interval

*CI for I² incalculable with one degree of freedom.

^aQuality of life scales and forest plot can be seen in figure 2. SF-36 scores converted to utility score using model EQ1 by Ara and Brazier(12), and standard deviations derived using a model by Wyld et al(13). If studies did not report a normative comparator and country and age-specific control data was readily available, we included them in the meta-analysis. When performing the meta-analysis without control data sourced externally to the studies from the systematic search, the following results were obtained: 5 studies, overall SMD -0.42 (CI -0.66, -0.17), I² 78% (CI 51, 88), τ² 0.09; 5 studies, transplant SMD -0.31 (CI -0.60, -0.02), I² 84% (CI 56, 91), τ² 0.09; 3 studies, dialysis SMD -0.67 (-0.97, -0.38), I² 0% (CI 0, 73), τ² <0.0001.

Although clustering (potential correlation from including subgroups taken from the same study) may underestimate between-study variance, the overall quality of life result showed a compensatory larger variance in effect size (τ² value). To overcome any effect of clustering, we also undertook a sensitivity analysis by meta-analyzing the treatment by modality interaction in studies that reported data for both transplant and dialysis patients (n=6). This showed a pooled difference in SMD between dialysis and transplant groups of -0.62 (CI -0.88, -0.37), I² 0% (CI 0, 61), τ² <0.0001. This was equivalent to the difference in effect estimates between transplant and dialysis presented in the table.

^bControl data from (35) used for UK patients from (72).

^cControl data from (39) used for (65).

^dControl data from (32) used for (28). Studies assessed affect using the Positive and Negative Affect Schedule.

^eRosenberg self-image scale scores were reported by (38) and were reversed to enable comparison; the Self-Perception Profile for Adolescents was reported by (21).

FIGURES

Figure 1. Systematic search results for studies examining social, psychological health and lifestyle outcomes for young adults receiving RRT, according to PRISMA guidelines

Figure 2. Forest plot of quality of life scale scores relative to healthy controls, by modality